INJECTABLE SOURCES OF LOCALLY CONTROLLED ELECTRICAL FIELDS TO FACILITATE TISSUE REPAIR

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Abstract - **Both pulsatile (AC) and continuous (DC) electrical fields have been reported to increase growth or healing or otherwise modify the structure of various tissues, including nerves, bones and skin. Systematic application of these techniques in both animal research and clinical treatment has been hampered by the limitations of currently available technology. We describe a new modular approach in which one or more wireless, microminiature, programmable current generators can be injected or implanted in a wide range of sites. Each device has its own address and can be powered and commanded via an external RF field to produce 10, 100 or 500 µA DC and/or pulse trains of 0.2–30 mA at 4–512 µs duration. The implants are 2 mm in diameter and 16 mm long. They are made from hermetically sealed, biocompatible materials, so they can be used indefinitely or left in situ after treatment is complete.**

Keywords - **regeneration, wound healing, direct current, electrical stimulation, BIONs**

I. INTRODUCTION

Electrical stimulation has been reported to be useful as an aid to wound healing, especially in recalcitrant pressure ulcers, infected wounds and chronic nonunion of long-bone fractures. Electrical bone growth stimulators are also currently the focus of attention as an adjunct to lumbar spinal fusion [1], and have been suggested as a possible tool in controlling the developmental growth deformities found in cleft lip & palate and craniofacial anomalies [2]. The requisite 'wiring' of the wounds presents a significant limitation in all of these applications, because of the concurrent morbidities associated with repeated interventions and the prolonged maintenance of percutaneous leads (infection, erosion, fistulae, scarring, lead breakage, lead migration, etc.). We describe a new modular technology that could overcome this limitation: one or more wireless, microminiature, programmable current generators can be injected in a wide range of sites (or implanted in open cases). Each device has its own address and can be powered and commanded via an external RF field to produce 10, 100 or 500 µA DC and/or pulse trains of 0.2–30 mA at 4–512 µs duration. The implants are 2mm in diameter and 16 mm long. They are made from hermetically sealed, biocompatible materials, so that they can be used indefinitely or left in situ after treatment is complete.

II. REVIEW OF APPLICATIONS

Electrical stimulation (ES) for clinical use can be delivered via various mechanisms: 1) direct injection of charge using metal electrodes in resistive contact with tissues; 2) induction of eddy currents in tissues by rapidly changing magnetic fields applied externally; 3) creation of electrostatic fields in tissues by high voltage external capacitive plates [3]. Low-frequency electromagnetic radiation has also been reported to affect organisms in various ways, but this remains controversial [4], and no obvious biophysical mechanisms exist to support this. Strategy 1, the direct injection of charge, can be subdivided functionally into AC currents whose charge density is low enough that the metal/electrolyte interface functions capacitively (in which case the biophysical mechanisms should be similar to strategy 2), and DC or high charge-density AC currents that reach the threshold for galvanic reactions at the metal/electrolyte interface, with the resultant possibilities of pH and oxygen effects, protein denaturation, heavy metal ion release, etc. For both types of charge injection, it is possible to create electrical fields in the tissue that are sufficient to evoke action potentials in excitable cells (which could give rise to a wide range of indirect effects), or sufficient to affect directly the growth and alignment of unexcitable cells, such as epithelial cells, fibroblasts, osteoblasts and neuroglia. In general, cells with elongated processes that span more of the field gradient are more likely to detect and perhaps respond to applied electrical fields.

Wound Healing: Electrical stimulation for chronic wound care has been reported to increase the rate of healing by more than 50%, as well as the total number of recalcitrant wounds successfully healed [5,6]. In 1994 the Agency for Health Care Policy and Research (AHCPR) reviewed ES for the treatment of pressure sores and recommended its use in severe and/or recalcitrant cases.

Bogie et al [5] reviewed applications of electrical stimulation specific to wound healing and pressure sore prevention. In order to establish optimal delivery techniques, they demonstrated in a pig model that DC stimulation was most effective for wound *area* reduction (at 127 µA.cm^{-2}), whilst AC stimulation proved superior for wound *volume* reduction (at 1,125 µA.cm^{-2}). An implanted stimulation system with percutaneous leads was utilized. The mechanisms proposed by the authors are both at a 'micro-environmental' level (electric field effects favoring tissue health variables such as vascularity and growth factors [5,7]), and also via the 'mechanical' benefits of ES (movement with pressure relief; muscle hypertrophy with improved pressure distribution).

Gardner et al [8] performed a meta-analysis of 15 studies to quantify the effects of electrical stimulation on wound healing. Healing rate (per week) was found to be 22% for the ES samples vs. 9% for the controls – an

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Abstract

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improvement of 144% (with non-overlapping 95% confidence intervals).

Mentes et al [9] investigated the influence of pulsed electromagnetic fields (PEMFs) on the mechanical strength and collagen content of uncomplicated colonic anastomoses in rats. A standardized left colonic resection was performed with end-to-end anastomosis. For three days after surgery, 3 randomly assigned groups were exposed to 100Hz PEMFs at various field strengths (1 or 2 mT) and duty cycles. Mean bursting pressure and hydroxyproline content were found to be elevated in all treated groups vs. an untreated control group. It is unclear whether the eddy currents induced by such magnetic fields would be sufficient to evoke action potentials in excitable cells.

Several hypothetical biophysical mechanisms have been advanced to account for the encouraging but largely empirical phenomena described [5]: 1) increases in DNA synthesis and protein transcription; 2) epithelial and fibroblast cell migration into wound sites; 3) altered membrane permeability; 4) spatial signals guiding tissue development (electro-chemotactic signals).

Bone Growth: Bone and other connective tissues in culture tend to orient their growth in the presence of low-density electrical field gradients. It has been hypothesized that similar potential gradients occur naturally in mechanically stressed tissues and serve to direct growth in vivo [10]. These phenomena have given rise to a variety of clinical methods for applying such fields to promote healing of difficult fractures, each associated with multiple reports of clinical benefits [11,12,13,14,15]. Both directly applied electrical fields and PEMFs have been associated with changes in cellular biochemistry (including activation of cyclic adenosine monophosphate (cAMP), which could affect most aspects of cellular metabolism); increased synthesis of protein and bone matrix; and tissue structural changes including vascularization and calcification [3]. Biophysical mechanisms proposed, include some that relate to local electrochemical processes occurring at the electrode-tissue interfaces themselves, and not exclusively to the field gradients induced by the applied currents. For example, a cathodic electrode consumes oxygen and releases hydroxyl ions ($2H_2O + 4e^- + O_2 = 4OH^-$), thereby lowering oxygen tension and increasing pH locally [3]. Such anaerobic conditions normally prevail and appear to encourage osteogenesis in both growth plates and fracture calluses [3].

Various empirical studies in animals and patients suggest an optimal range of DC intensity (around 5-20 mA) that induces osteogenesis in the vicinity of the negative electrode [16,17]. Most of these have focused on healing chronic nonunions of mature long (cortical) bones rather than affecting growth in membranous bones. Furthermore, it is difficult to relate the current applied to actual current density achieved in the target tissues. Tissue culture of osteoblast-like cell lines has demonstrated substantial acceleration of cellular proliferation and calcification at 100 $\mu A.cm^{-2}$ DC, in patterns that appear similar to those occurring in ossification centers of normal membranous bone [18].

Nerve Regeneration: Transected axons in the *central* nervous system generally do not regenerate. There have been various attempts to use electrical fields to overcome this limitation, but current research is focused rather on pharmacological and cellular strategies to overcome what appear to be a variety of barriers to CNS regeneration. Transected axons in *peripheral* nerves, however, regenerate readily, albeit slowly. DC electrical fields appear to accelerate and direct outgrowth of neurites in culture, and may be useful in accelerating clinical nerve regeneration [19], although clinical applicability remains uncertain. In mixed nerves, regenerating axons commonly enter inappropriate pathways [20], contributing to the poor functional recovery seen so often, despite remarkable advances in microsurgical nerve repair techniques, operator experience and rehabilitation therapies. Abdulhakeem et al [21] employed short-term (1–20 hr) electrical stimulation sufficient to evoke antidromic action potentials in motor axons of surgically repaired rat femoral nerves. One hour of 20 Hz stimulation at the time of repair resulted in accelerated and preferential motor reinnervation at 3 weeks. This favorable effect could be prevented by tetrodotoxin blockade of antidromic conduction to the cell body, suggesting that the effects were centrally mediated. Proposed mechanisms include: 1) depolarization-induced Ca^{++} entry into the cells associated with upregulation of immediate early genes, initiation of gene expression and neurite outgrowth; 2) enhanced production of the neurotrophin BDNF (brain-derived neurotrophic factor), and its receptor TrkB (both mRNA and protein levels for these substances are increased following axotomy, indicating enhanced transcription).

PEMFs have been used to enhance regeneration of transected facial nerves in rats [22], but it is difficult to separate the possible effects of direct excitation versus those of subthreshold field gradients which could exert trophic effects via the various cellular mechanisms as discussed above.

III. CAPABILITIES OF THE BION TECHNOLOGY

A new class of implantable medical devices, 'BIONic Neurons', has recently been developed [23]. These wireless microstimulators provide a safe, effective, precise and potentially inexpensive means of applying well-controlled electrical fields to local sites. One or more separately addressable BIONs can be injected into the body through a 12 gauge needle, where they receive power and digital command data from a single external RF coil. The components of this system are detailed elsewhere [23].

BIONs are designed to deliver brief current pulses suitable for exciting action potentials in neurons. This is normally accomplished through charge-balanced AC waveforms, allowing the metal electrodes to act as capacitive interfaces with the tissues and so avoiding electrochemical reactions. BIONs employ an unusual mode of power storage in which a preanodized tantalum electrode acts as an electrolytic capacitor with respect to body fluids, with a nonpolarizing counter-electrode of iridium. The BION output circuitry can be commanded to produce variable levels of DC (10, 100 or 500 µA) until the voltage across this electrolytic capacitor reaches the

+17 VDC compliance voltage of its power supply. We undertook to assess whether this circuitry could be suited to delivering continuous DC on the order of 400 µA (see below) via an unanodized tantalum or platinum anode. We assessed first the anodization rate of an unanodized tantalum anode in phosphate buffered saline solution at a compliance voltage of 17 VDC and an anodizing current of 100 µA (with a platinum cathode). By introducing a range of series resistances initially, we calibrated a Current-Impedance curve against which to determine our developing impedance from the measured current as anodization occurs. As expected from Ohm's law, the current delivery began falling off in the region of 170 kOhm. Measuring current delivery over time demonstrated that this scenario could only deliver constant DC at 100 µA for less than 36 hrs before the anodization resistance exceeded the compliance voltage's ability to maintain this current level.

The BION circuitry could, however, be adapted to generating longer-term DC by employing either of the folowing 2 possible approaches:

1) The tantalum anode could be replaced by a noble metal electrode (e.g. platinum), provided it were of sufficient surface area to avoid excessive electrolytic damage to the electrode and surrounding tissues.

2) Quasi-DC could be produced via the tantalum capacitor electrode during the lengthy recharge phase following a strong pulsatile discharge. This avoids the confounding effects of electrolytic reactions at either electrode, but does introduce potentially confounding effects during the brief periods of intense field reversal, with possible activation of ionic channels in excitable cells (which may, in fact, be a favorable mechanism for enhancing peripheral nerve regeneration, as noted above).

The present BION1 operates only in the presence of a 2 MHz RF field that inductively energizes its circuitry. For chronic treatments it would be desirable to have implants that could generate the requisite currents autonomously for at least part of the day. Thus we have analyzed the feasibility of a third option for delivering long-term DC: that of powering somewhat larger BIONs with a lithium ion battery which could be recharged via the inductively powered circuit when convenient (e.g. nocturnally):

- The literature suggests a therapeutic current density of approximately 100 µA.cm^{-2} DC [18].
- The current density around a bipolar source in volume conductive tissue tends to be homogeneous over a distance about equal to the electrode spacing, but falling rapidly at greater distances from the bipolar axis.
- If the electrodes were at the ends of a BION about 2cm long, the required output current would be of the order of 400 µA.
- The DC resistance of the tissue between BION electrodes is about 1 kOhm, resulting in a 0.4 V potential gradient.
- If both electrodes are operated galvanically, they will

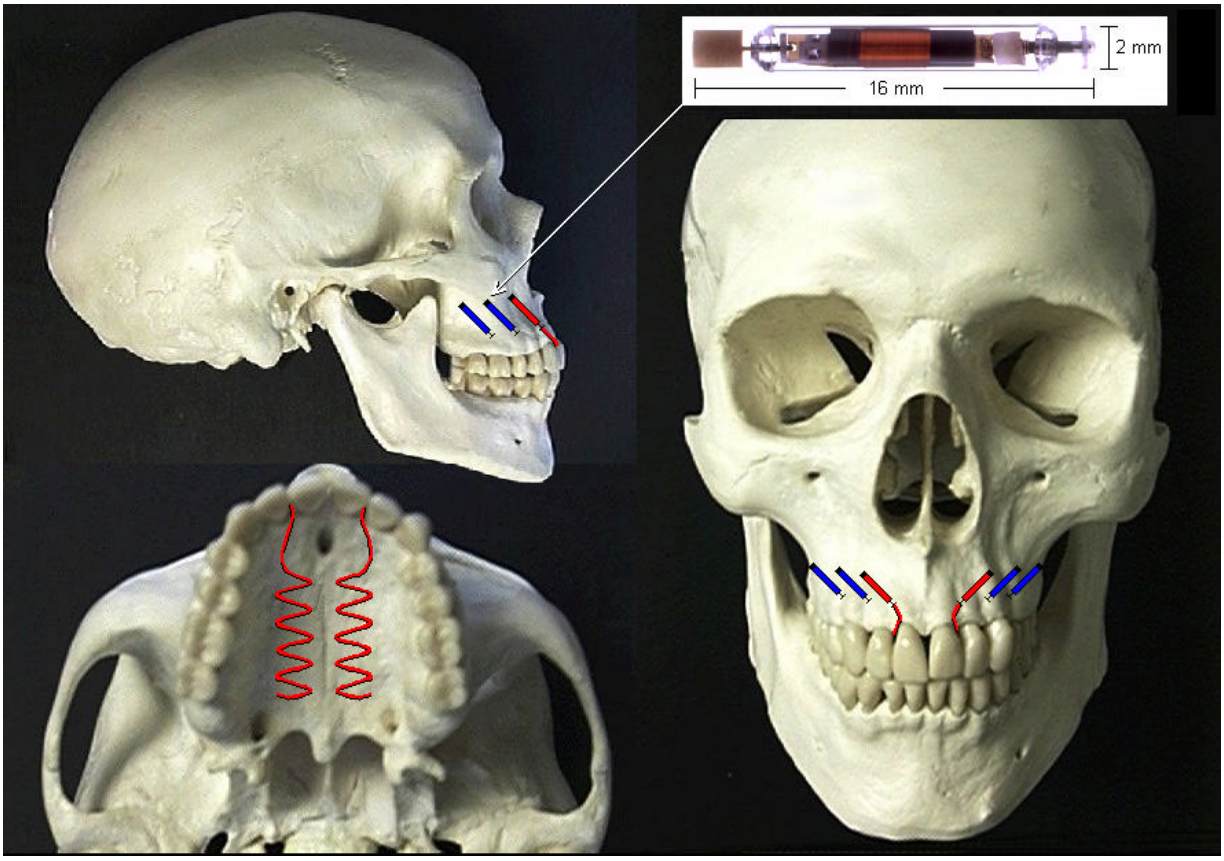

Fig.1 - An injectable system of BIONs ("BIONic Neurons") could potentially be harnessed to promote bone growth differentially at selective epiphyses and ossification centers in cases of abnormal pediatric development [2]. Potential applications include a host of congenital craniofacial and somatic developmental anomalies for which the current gold standard is highly invasive distraction osteogenesis. Shown here is a representation of "Developmental Osteogenic Stimulation" [2] being used to direct and promote maxillary and palatal shelf growth following cleft lip & palate repair.

each require a 0.8 V polarization.

- The compliance voltage needed to generate the required current will thus be 0.8 + 0.8 + 0.4 = 2.0 VDC, which can be provided by a lithium cell (3.0–3.3 VDC).
- The power drawn from the battery is the product of the voltage (3 V) and the current (400 µA stimulation + ~20 µA quiescent circuit requirement) = 1.26 mW.
- Current Li-ion battery technology will provide about 250 mWh.cm^{-3}, so that a 16 h charging cycle would require a 0.08 cm^3 battery.
- In a BION enlarged to a diameter of 3mm (from 2 mm), the battery would require 11.3 mm of length.
- Assuming the remaining circuitry, packaging and electrodes occupied 50% of the volume, the overall dimensions should be about 3 mm in diameter x 23 mm in length, which would be suitable for implantation in many sites (e.g. Fig. 1), and would be compatible with the current density requirement as computed above.

IV. Discussion

Currently 2 classes of BION are under development [23] : BION1 generates stimulation pulses of 0.2–30 mA at 4–512 ms duration. Each device is separately addressable (up to 256), and these are now being used in clinical trials for Therapeutic Electrical Stimulation (TES) to prevent and reverse disuse atrophy in stroke and arthritis patients. BION2 will sense muscle length, limb acceleration and bioelectrical potentials for sensory feedback control of Functional Electrical Stimulation (FES). These are currently under development.

We have shown that BION1 technology could relatively easily be adapted to generate low current DC output of the order of 100 µA over several months either by utilizing a noble metal anode or, in the current configuration, through periodic strong pulsatile discharge of its capacitor electrode. Such arrangements would be suited to treatment of recalcitrant ulcers, soft-tissue wounds and following nerve repair.

For longer term DC functionality, rechargeable battery-operated BIONs with platinum or possibly carbon electrodes are a feasible alternative. These devices would be suited to nocturnal charging by an RF coil in an underblanket or pillow for example, and could prove especially useful in cases of bony pathology with their associated requisite longer treatment periods. Because BIONs are hermetically sealed and consist of biocompatible materials, they can be used indefinitely or left in situ after treatment is complete.

V. Conclusion

Electrical currents can influence the growth of a wide range of tissues by various biophysical mechanisms. Limitations in the technologies available have made it difficult to establish optimal therapeutic parameters empirically, or to distinguish among hypothesized biophysical mechanisms so as to enable accurate predictions based on theory. BIONs, either in their current form or feasible variants, could facilitate the studies necessary to resolve these questions and could provide the basis for routine clinical treatment of a wide range of tissue and growth abnormalities using electrical currents.

References

[1] D. Marchac & E. Arnaud, "Midface Surgery from Tessier to distraction," *Childs Nerv Syst*, vol. 15:11-12, pp. 681-694 , Nov. 1999.

[2] H.M. Kaplan, "'Developmental Osteogenic Stimulation' – An Alternative to Distraction Osteogenesis? (feasibility analysis)," *Grodin's Graduate Research Symposium*, University of Southern California, A.E. Mann Institute for Biomedical Engineering, Los Angeles, CA 90089 USA, 2001.

[3] M. Oishi & S.T. Onesti, "Electrical Bone Graft Stimulation for Spinal Fusion - A Review," *Neurosurgery*, vol. 47:5, pp. 1041-1056 , Nov. 2000.

[4] R.M. Macklis, "Magnetic Healing, Quackery, & the Debate About the Health Effects of Electromagnetic Fields," *Annals of Internal Medicine*, vol. 118(5), pp. 376-383, March 1993.

[5] K.M. Bogie et al, "Electrical Stimulation for Pressure Sore Prevention & Wound Healing," *Asst Technol*, vol. 12, pp. 50-66, 2000.

[6] A. Sheffet et al, "Applying Electric & Electromagnetic Energy as Adjuvant Treatment for Pressure Ulcers: A Critical Review," *Ostomy Wound Management*, vol. 46(2) pp. 28-44, 2000.

[7] R.J. Fitzsimmons et al, "Frequency dependence of increased cell proliferation, in vitro, in exposures to a low-amplitude, low-frequency electric field: Evidence for dependence on increased mitogen activity released into culture medium," *Journal of Cell Physiology*, vol. 139, pp. 586-591, 1989.

[8] S. Gardner et al, "Effects of Electrical Stimulation on Chronic Wound Healing: a Meta-analysis," *Wound Repair & Regeneration*, vol. 7, pp. 495-503, 1999.

[9] B.B. Mentes et al, "Influence of Pulsed Electromagnetic Fields on Healing of Experimental Colonic Anastomosis," *Diseases of the Colon & Rectum*, vol. 39(9), pp. 1031-1038, Sept. 1996.

[10] Z.B. Friedenberg & C.T..Brighton, "Bioelectric potentials in bone," *J Bone Joint Surg Am*, vol. 48A, pp. 915-923, 1966.

[11] C. Jervey & R.J. Friedman, "Electrical Stimulation - Current concepts & indications," *Contemp Orthop*, vol. 20, pp. 61-65, 1990.

[12] I. Izabakarov & B.P. Markov, "The effect of dissimilar metals (galvanic current) on bone tissue status," *Stomatologiia* (Mosk), vol. 72:2, pp. 19-22, April 1993 [Language of Publication: Russian].

[13] M. Cohen et al, "Totally implanted direct current stimulator as treatment for a nonunion in the foot," *J Foot Ankle Surg*, vol. 32:4, pp. 375-81, July 1993.

[14] F.X. Hart, "Spreadsheet method for calculating the induced currents in bone-fracture healing by a low-frequency magnetic field", *Bioelectromagnetics*, vol. 15:5, pp. 465-82, 1994.

[15] M. Steiner & W.K. Ramp, "Electrical stimulation of bone & its implications for endosseous dental implantation," *J Oral Implantol*, vol. 16:1, pp. 20-7, 1990.

[16] Z.B. Friedenberg et al, "Bone reactions to varying amounts of direct current," *Surg Gynecol Obstet*, vol. 131, pp. 894–899, 1970.

[17] Z.B. Friedenberg et al, "The response of non-traumatized bone to direct current," *J Bone Joint Surg Am*, vol. 56A, pp. 1023–1030, 1974.

[18] Q. Wang et al, "Osteogenesis of Electrically Stimulated Bone Cells Mediated in Part by Calcium Ions," *Clinical Orthopaedics & Related Research*, vol. 348, pp. 259-268, March 1998.

[19] S.M. Hanson & M.E. McGinnis, "Regeneration of rat sciatic nerves in silicone tubes: characterization of the response to low intensity d.c. stimulation," *Neuroscience*, vol. 58(2), pp. 411-21, Jan. 1994.

[20] S. Sunderland, *Nerve & Nerve Injuries*, Churchill Livingstone: London, 1978.

[21] A.A.M. Abdulhakeem et al, "Brief Electrical Stimulation Promotes the Speed & Accuracy of Motor Axonal Regeneration," *Journal of Neuroscience*, vol. 20(7), pp. 2602-2608, April 2000.

[22] J.M. Byers et al, "Effect of Pulsed Electromagnetic Stimulation on Facial Nerve Regeneration," *Archives of Otolaryngology - Head & Neck Surgery*, vol. 124(4), pp. 383-389, April 1998.

[23] G.E. Loeb et al, "BION System for Distributed Neural Prosthetic Interfaces," *Medical Engineering and Physics*, vol. 23, pp. 9-18, 2001.